REMARKS

By the foregoing amendment applicant has amended each of the independent claims 1 and 3, recite that the pharmaceutical product is used in the treatment of inflammatory or respiratory disease, and further defines the therapeutic agents as provided in particulate form "having a particle size from non-size up to about 12μm". Support for each of these amendments can be found in the original disclosures for example, page 1 second paragraph, page 2 first full paragraph, forth full paragraph, page 4 third full paragraph and page 5 sixth full paragraph (all references to the published WO 004/019985 application. Claim 18 has also been amended to proved antecedent basis for a term used in dependent claim 19.

Also, by the forgoing amendment applicant has cancelled the claims to the non-elected invention i.e., claims 10-14 and 27-33, but expressly reserved their rights to file one or more divisional application (s), claiming the benefits afforded by 35 U.S.C. 119, 120 and 121.

Reconsideration of the previous rejection of claims 1-2 under 35 U.S.C. 112 first paragraph, is respectfully requested.

As noted hereinabove, claim 1 has been amended to recite treatment of "inflammatory or respiratory diseases" and thus the claims are enabled by the specification which provides a teaching for the same.

The specification also provides support for the "3-in-1 combination therapy" as found on page 2, fourth full paragraph, and particularly describes the claimed pharmaceutical products beginning at the foot of page 2, through the middle of page 4, as well as on pages 6-9. Exemplification of various combinations of 3-in-1 compositions are found beginning at the top of page 10 and proceeding through Examples 1-43, of the following pages.

Accordingly, applicants have clearly provided not a only written description of the claimed invention, but also working examples of the particularly specified claimed compositions so as to enable any person having ordinary skill in the art to make and use the

compositions so as to enable any person having ordinary skill in the art to make and use the invention in the fields specified. Withdrawal of the rejection is therefore respectfully requested.

Reconsideration of the previous rejections of claims 1-9, and 15-26, under 35 U.S.C. 102 (e), as being anticipated by Meade et al. (U.S. Patent Publication 2003/0018019 A1) is respectfully requested.

In order to constitute anticipation, the reference must teach every element of the claim.

In fact, the USPTO has promulgated to Examiners exemplary teachings of what does and does, not, constitute anticipation See generally, MPEP Section 2131.

As set forth in this section the Examiners are instructed that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (citations omitted)." Meade et al. does not anticipate the claimed invention.

As noted hereinabove, in amending the claims to comply with 35 U.S.C. 112, the claims have been amended to recite that the composition is in particulate form, having a particle size ranging from nano-size up to about 12μm. In particular, there is no explicit disclosure in Meade et al of a pharmaceutical product comprising any of the claimed combination of active ingredients where the active ingredients have a particle size range of from nano-size up to about 12μm, as recited in the present claims. Although applicants note example 2 of Meade et al, there is no teachings in this Example to use particle sizes from nano-size up to about 12μm. The example is completely silent on particle size, as is the rest of the Meade et al. publication. Thus, there can be on anticipation of the claims by the Meade et al. reference. Withdrawal of the rejection is therefore respectfully requested.

Reconsideration of the previous rejection of claims 1-9, 15-22, and 24-26, under 35 U.S.C. 103 (a), as being unpatentable over Keller et al. (U.S. Patent 6,645,466 B1), is

respectfully requested. Keller et al. is concerned with the problem of poor moisture resistance of dry powder formulations. This does not really address the problem of providing improved treatments for inflammatory or respiratory diseases, which is the problem addressed by the present application.

As one skilled in the art would understand the point Keller et al. is not to any particular combination of active ingredients, but rather to the generally principle of using magnesium stearate in a dry powder inhalation (DPI) formulation. Although various active ingredients are mentioned, this is really only in passing. Particular active/combination of active ingredients are irrelevant to the invention of Keller et al. Rather the invention of Keller et al is a general application to any drug in a (DPI) formulation and, in contrast to the present invention, the particularly recited active ingredients, or combination of active ingredients, are not required. Thus, a skilled person would not have looked to this document in considering the problem solved by this present invention, and it simply does not relate to the field to which the present invention relates, nor have any teachings which would make obvious the instantly recited claimed subject matter which are specified as particular combinations of active ingredients, in a particulate form, having a particle sizing ranging from about nano-size up to about 12μm.

It appears that the Examiner clearly recognizes the deficiencies in the disclosure of Keller et al., in failing in exemplifying a formulation containing a beta-mimetic, an anti-cholinergic, and/or a corticosteroid, as noted by the first full paragraph, on page 14 of the Office Action.

Although it is alleged that Keller et al. teach a formulation that can contain two or more pharmaceutically active compounds, such is neither a teaching or a suggestion of the claimed subject matter. Keller et al. is simply insufficient to establish as obvious the claimed invention at the time the invention was made. As noted hereinabove, in response to the rejection of the instant claims under 35 U.S.C. 112, first paragraph, Keller et al. simply is not

ingredients can be used in a single formulation. One skilled in the art would not know with particularity how to arrive at the claimed subject matter from the teachings of Keller et al. While applicant has specified (and exemplified) various active ingredient combinations, Keller et al. does not do so. Applicants have provided an enabling disclosure for particularly described combination of 3-in-1 formulations, while Keller et al. does not provide an enabling disclosure of any 3-in-1 formulations meeting applicant's claims. Thus, Keller et al. simply does not make the claimed invention obvious to one having ordinary skill in the art. Keller et al. example formulations contain only one active ingredient (and not a combination of three) active ingredients as in the claimed invention. Similarly, all Keller et al. claims are to a formulation containing a single active ingredient only.

Moreover, applicants does not agree the Examiner's view that it would have been obvious to vary the Keller et al. teachings so as to formulate any combination of the active ingredients mentioned therein as aerosol formulations. Keller et al. relates specifically to dry powder formulations and dry powder formulations are the whole point of Keller et al invention. It would therefore not have been obvious to one having ordinary skill in the art to formulate aerosol formulations because to do so would go against the explicit teachings of the document to use dry powders. Moreover, regarding the point about particle size, particle sizes having a size outside the claimed range, do not give satisfactory dose and efficiency. Particles having a size above 12 microns are too large to penetrate adequately into the lungs. Thus, particles thus having a size smaller than 12 microns are required for effective lung penetration, as larger particles are readily trapped in the mouth and/or upper airway passages, and when trapped,the active ingredients are not absorbed therein. In order for the active ingredients to be effectively absorbed, deep lung penetration is required, suitable penetration into the alveoli (i.e., the small air sacs of the lungs) where a very large surface area for absorption is available. All particles having a size above 12 microns, may penetrate to the tracheobronchial regions, in the upper airways, these large particles do not penetrate into the

association with halving the dose of fluticasone propionate in severe asthmatics leads to small improvements and effort dependent and independent pulmonary functions outcomes, but not quality of life scores".

This is actually a surprising result, since tiotropium has not previously been considered effective in asthma treatment (See page 12, second paragraph). This improvement for severe asthmatics is a surprising and unexpected effected, and would not have been predicted on the basis of any of the cited prior art in the Office Action. It is recognized in the paper that on the basis of the present results, there may now be a role for tiotropium in the treatment of severe asthma (See final paragraph of discussion). This role had not previously been recognized.

The triple-active combination of the presentinvention also let t a significant reduction in the exhaled level of nitric oxide, in addition to the "steroid-sparing" effect. In this context, applicants refer to page 12, first paragraph of the paper. Nitric oxide is a prominent measure of inflammatory processes in the lungs, and so can be used as a marker for information in asthma. The triple-active combination of the present invention led to suppression of the level of exhaled nitric oxide, and significant improvements of FEVI and FVC, indicating an improvement in lung function. This effect is not seen with simply double-active combinations, for example, it is not seen with fluticasone and salmeterol alone (See second paragraph, page 11). Again this is a surprising effect for the tripe-active combination.

It is believed that the effects shown in the attached study are "class" effects-that is, it is believed that these effects are seen with all of the claimed triple-active combinations. These all include two bronchodilators, acting in different ways, together with a steroid. The authors of the enclosed paper state that "the concept of safe step down of inhaled cortico steroid with the addition long-acting brochodilators can be supported in this cohort of severe patients..." See Discussion. It is clear that the results are not specific to any particular

which would be seen with all the claimed combinations. Accordingly, all the claimed combination of the instant invention, are linked by the same general inventive concept: the combination share the steroid-sparing effect. Applicants believe that they should be entitled to protect all the specifically claimed combinations. For the foregoing reasons withdrawal of the prior art rejections are respectfully requested.

Reconsideration and withdrawal of the provisional non-statutory double patenting rejections of the obvious type are respectfully requested. Although it is alleged in the Office Action that the application claim is either anticipated by, or would have been obvious over the referenced claims of co-pending application 11/574,902 (hereinafter "Lula '902 application") in view of Meade et al., applicants respectfully disagree.

As noted above Meade et al. does not show composition in particulate form having a particle size from nano-size up to about 12μm. Furthermore, the Lula '902 application does not teach addition of corticosteroids.

As noted in the discussion above with regard to the attached paper, the absence of the steroid is a critical absence in the claimed invention. The claimed invention, in treating inflammatory or respiratory diseases, has a steroid-sparing effect, because of the presence of the two bronchodilators, in combination with the steroid. When no steroid is present, as in Lula '902, the effect of the present invention would not be seen. Meade et al. does not suggest a composition having the 3-in-1 active ingredient as specifically recited, in combination, with the particle size combination which permits administration of the drug to reach the alveoli because of the particle size range as recited in the claims. Thus, any teachings of Lula '902 application and/or Meade et al. would be difficult for anticipation, nor make obvious the claimed invention. Accordingly, the applicants respectfully request that the provisional obviousness type double patenting be withdrawn and furthermore note that as the conflicting claims have not in fact been patented, Lula '902 is not appropriate as a reference in a double patenting rejection of the obviousness type.

that as the conflicting claims have not in fact been patented, Lula '902 is not appropriate as a reference in a double patenting rejection of the obviousness type.

Having fully responded to the preceding Office Action, favorable reconsideration withdrawal of all grounds of rejections set forth therein are respectfully requested and prompt Notice of Allowance are earnestly solicited.

For the foregoing reasons, favorable reconsideration and withdrawal of the previous rejection and passage of the application to issue are respectfully requested.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 14-1437, under Order No. 8693.006.US0000.

Respectfully submitted,

Date: February 13, 2009

Attachment: As noted above

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